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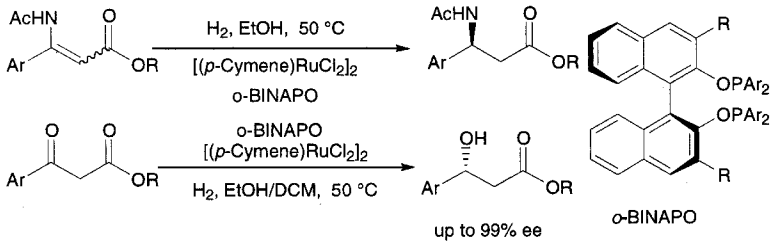

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Highly Effective Chiral Ortho-Substituted BINAPO Ligands (*o*-BINAPO): Applications in Ru-Catalyzed Asymmetric Hydrogenations of β-Aryl-Substituted β-(Acylamino)acrylates and β-Keto Esters

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During the last several decades, many effective chiral bisphosphines have been developed. However, there is no solution in dealing with many transition metal-catalyzed asymmetric transformations since enantioseletivities are often substrate-dependent. Subtle changes in conformational, steric, and electronic properties of chiral ligands can lead to dramatic variations of reactivities and enantioselectivities. Conformationally rigid and tunable chiral ligands offer a great advantage for optimizing the enantioselectivty of a reaction. Herein, we like to report ruthenium catalysts with a novel family of BINOL-derived phosphinite ligands for the first highly enantioselective hydrogenation of β-aryl-substituted β-(acylamino)acrylates. These catalysts are also effective for highly enantioselective hydrogenation of β-aryl-substituted β-keto esters.

Noyori and co-workers have demonstrated that highly skewed BINAP was an effective ligand for many asymmetric catalytic reactions.[1,2] A comparison of the structure of BINAP with the less-effective BINAPO ligands[3] reveals two possible reasons: (1) the oxygen atoms in the BINAPO increase the distance between the chiral binaphthyl moiety and PPh_2 groups and therefore decrease the influence of chiral binaphthyl on orientation of the phenyl groups of PPh_2 and (2) the presence of the C−O−P bond in BINAPO increases the flexibility of backbone. To develop highly effective BINAPO ligands, we have designed ligands **2a**−**d** by introducing groups into 3,3′-positions of the binaphthyl backbone (ortho-substituted BINAPO, abbreviated as *o*-BINAPO): introduction of 3,3′-R groups can restrict the orientation of Ar groups adjacent to phosphine atoms. In addition, tuning of the steric and electronic properties can be achieved by changing the R and Ar groups of ligands. These ligands can be synthesized from the corresponding diols [4] (Scheme 1).

Enantiomerically pure β-amino acids and their derivatives are important building blocks for the synthesis of β-peptides, β-lactam antibiotics, and many important drugs.[5] Recently, several synthetic methodologies have been developed to make β-amino acids by using stoichiometric chiral auxiliaries and catalytic methods,[6] Among these methods, straightforward asymmetric hydrogenation of β-aminoacrylic acid derivatives represents one of the simplest routes. Previous attempts at asymmetric hydrogenation of β-(acylamino)-acrylates using Ru[7] and Rh[8] catalysts led to moderate to good enantioselectivity. The main issue is that the different catalytic behaviors (ee values, catalytic activities) exist with *Z*- and *E*-isomeric substrates. For example, (*E*)-methyl 3-acetamido-2-butenoate gave 96% ee in Noyori's Ru-BINAP system,[7] while (*Z*)-methyl 3-acetamido-2-butenoate gave only 5% ee with the opposite configuration. So far, only moderate ee can be obtained with Rh-DuPhos[8c] and Ru-BINAP[7] systems for hydrogenation of β-aryl-substituted β-(acylamino)acrylates.

Scheme 1

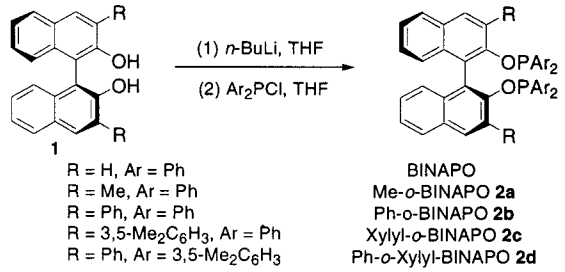
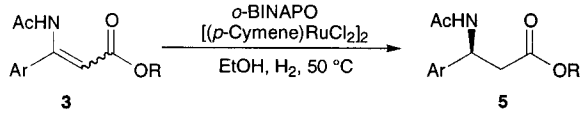


Table 1. Asymmetric Hydrogenation of β-Aryl-Substituted β-(Acylamino)acrylates **3**[a]



entry	ligands	Ar of **3**	R of **3**	ee (%)[b]	config.[c]
1	BINAPO	Ph	Me (**3a**)	2 (**5a**)	S
2	**2a**	Ph	Me (**3a**)	22 (**5a**)	S
3	**2b**	Ph	Me (**3a**)	98 (**5a**)	S
4	**2c**	Ph	Me (**3a**)	99 (**5a**)	S
5	**2d**	Ph	Me (**3a**)	97 (**5a**)	S
6	BINAP	Ph	Me (**3a**)	31 (**5a**)	S
7	MeO-Biphep	Ph	Me (**3a**)	39 (**5a**)	S
8	**2c**	*p*-F-C_6H_4	Me (**3b**)	99 (**5b**)	S
9	**2c**	*p*-Cl-C_6H_4	Me (**3c**)	97 (**5c**)	S
10	**2c**	*p*-Br-C_6H_4	Me (**3d**)	97 (**5d**)	S
11	**2c**	*p*-Me-C_6H_4	Me (**3e**)	99 (**5e**)	S
12	**2c**	*p*-MeO-C_6H_4	Me (**3f**)	99 (**5f**)	S
13	**2c**	*o*-Me-C_6H_4	Me (**3g**)	96 (**5g**)	S
14	**2c**	*o*-MeO-C_6H_4	Me (**3h**)	80 (**5h**)	S
15	**2c**	Ph	Et (**3i**)	98 (**5i**)	S
16	**2c**	*p*-F-C_6H_4	Et (**3j**)	98 (**5j**)	S
17	**2c**	*p*-Cl-C_6H_4	Et (**3k**)	95 (**5k**)	S
18	**2c**	*p*-Br-C_6H_4	Et (**3l**)	93 (**5l**)	S

[a] The absolute configurations were determined by comparing optical rotations with reported values. The reaction was carried out under 80 psi of H_2 in EtOH at 50 °C for 20 h, substrate/[Ru(*p*-cymene)Cl_2]$_2$/ligand = 50/1/2.1. [b] The ee (%) values were determined by GC using a chiralselect 1000 column. [c] Determined by the sign of rotations.

To test the synthetic utility of bisphosphinite ligands **2**, we have explored the Ru-catalyzed asymmetric hydrogenation of β-aryl-substituted β-(acylamino)acrylates **3** (Table 1). Substrates **3a**−**l** (*E*/*Z* = 5/95 to 40/60) can be made from the β-keto esters **4** according to a literature procedure.[8c,9] The *E*/*Z* mixture of enamides **3a**−**l** cannot be separated by silica gel column chromatography. The Ru catalyst was prepared by mixing the [Ru(*p*-cymene)Cl_2]$_2$ and a

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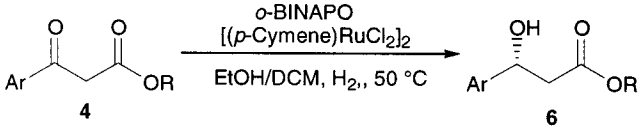
Table 2. Asymmetric Hydrogenation of β-Keto Esters **4**[a]



entry	ligand	Ar of **4**	R of **4**	ee (%) of **6**[b]	config.[c]
1	**2c**	Ph	Et (**4a**)	99 (**6a**)	R
2	**2c**	*p*-F-C_6H_4	Et (**4b**)	93 (**6b**)	R
3	**2c**	*p*-Cl-C_6H_4	Et (**4c**)	98 (**6c**)	R
4	**2c**	*p*-Br-C_6H_4	Et (**4d**)	96 (**6d**)	R
5	**2c**	*p*-Me-C_6H_4	Et (**4e**)	95 (**6e**)	R
6	**2c**	*p*-MeO-C_6H_4	Et (**4f**)	87 (**7f**)	R
7	**2c**	*o*-Me-C_6H_4	Et (**4g**)	90 (**6g**)	R
8	**2c**	*o*-MeO-C_6H_4	Et (**4h**)	98 (**6h**)	R
9	**2d**	Me	Me (**4i**)	96 (**6i**)	S
10	**2d**	Me	Et (**4j**)	96 (**6j**)	S
11	**2d**	$ClCH_2$	Et (**4k**)	98 (**6k**)	R

[a] The absolute configurations were determined by comparing optical rotations with reported values. The reaction was carried out under 80 psi of H_2 in EtOH/DCM (3/1) at 50 °C for 20 h, substrate/[Ru(*p*-cymene)Cl_2]$_2$/ligand = 200/1/2.1. [b] The ee (%) values were determined by GC using a chiralselect 1000 column or HPLC with Chiralpak AS column. [c] Determined by the sign of rotations.

bisphosphinite ligand **2** in situ in hot DMF.[10] The reaction was carried out under 80 psi of H_2 in EtOH at 50 °C for 20 h. Although ligands BINAPO and **2a**−**d** show similar reactivity, the enantioselectivity varied dramatically. For example, substrate **3a** was reduced with 2% ee using a Ru-BINAPO complex as the catalyst (entry 1). The enantioselectivity increased to 22% with Ru-Me-*o*-BINAPO (**2a**) (entry 2), Surprisingly, ee values increased dramatically when an aryl was introduced in the *o*-BINAPO ligand (entries 3−5). Up to 99% ee has been achieved with the Ru-**2c** catalyst (entry 4). This result is superior to ee values obtained with other phosphine ligands (entry 6, 31% ee with BINAP; entry 7, 39% ee with MeO-BIPHEP).

A variety of β-aryl-substituted β-(acylamino)acrylates were employed as substrates for the Ru-catalyzed hydrogenation reaction with **2c** as the ligand (Table 1). High enantiomerical excesses have been achieved with the exception of **3h** (entry 14). There is no major electonic effect on the substitution pattern of **3** (96−99% ee). A possible explanation of the low ee (80%) with *o*-methoxy-substituted enamide **3h** is that competing coordination of the *o*-methoxy group exists in the Ru system. In this catalytic system, methyl β-aryl-substituted β-(acylamino)acrylates gave slightly better enantioselectivities than the corresponding ethyl β-aryl-substituted β-(acylamino)acrylates.

It is noteworthy that *our catalytic system Ru-bisphosphinite can tolerate an E/Z mixture of substrates*. The ability to reduce the *E*/*Z* mixture of β-aryl-substituted β-(acylamino)acrylates **3** is crucial to practical synthesis of various β-aryl-substituted β-amino acids. To the best of our knowledge, *enantioselectivities achieved with Ru-2c as the catalyst for hydrogenation of 3 are the highest reported to date*.

In a related area, Ru-BINAP[1,2] and other Ru-phosphine systems[11] were efficient for reduction of β-alkyl-substituted β-keto esters, but only moderate to good enantioselectivities were obtained for hydrogenation of β-aryl-substituted β-keto esters.

To further expand the utility of the *o*-BINAPO ligands system, we have examined Ru-catalyzed enantioselective hydrogenation of β-aryl-substituted β-keto esters (Table 2). High enantioselectivities have been achieved with most substrates (93−99% ee) except for **4f** and **4g**. Under the same reaction conditions, we examined the enantioselectivties for hydrogenation of **4a**: BINAP (80% ee), MeO-BIPHEP (88%), BINAPO (29%), **2a** (29%), **2b** (94%), **2c** (99%), and **2d** (97%). *The enantioselectivities achieved with Ru-2c as the catalyst are the highest reported for substrate 4a*. For hydrogenation of β-alkyl-substituted β-keto esters, we found that *o*-BINAPO (**2d**) is a better ligand (entries 9−11).

In conclusion, we have developed a novel family of chiral bisphosphinite ligands for enantioselective Ru-catalyzed hydrogenation. These catalysts are especially effective for hydrogenation of β-aryl-substituted β-(acylamino)acrylates and β-aryl-substituted β-keto esters. The highly enantioselective hydrogenation provides a useful way to prepare β-aryl-substituted β-amino acids and β-hydroxyl acids. Further studies of other transition metal complexes of these ligands and their applications are in progress.

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Supporting Information Available: Full experimental procedure, GC, HPLC data, and $[\alpha]_D$ values of ligands **2** and hydrogenation products **5** and **6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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